
Conformational Searching of Transition Metal Compounds

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ABSTRACT: To date, no conformational search of inorganic complexes has been reported that searches for all the conformations and configurations available to the complex. This is due to the various coordination geometries that transition metal ions can adopt and the difficulties in conducting conformational searches with systems that have connected ring systems, such as the ones formed when a metal ion binds a multidentate ligand. Using three test complexes $[\text{Co}(\text{dien})_2]^{3+}$, $[\text{Co}(\text{dien})(\text{dpt})]^{3+}$, and $[\text{Co}(\text{hexamethylcyclam})(\text{Cl})_2]^+$ the ability of the random kick (Cartesian stochastic Monte Carlo search) method and the Monte Carlo dihedral and positional method to find all conformations and geometric isomers was tested (dien, diethylenetriamine; dpt, di(3-aminopropyl)amine; hexamethylcyclam: tet-a, *meso*-5,5,7,12,12,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane; tet-b, *racemic*-5,5,7,12,12,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane). Both methods are significant improvements on the current method by which all possible isomers are entered graphically and minimized individually. The major difficulty that was encountered was how to differentiate between the large number of similar conformations found. © 1999 John Wiley & Sons, Inc. J Comput Chem 20: 1549–1558, 1999

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Introduction

Most modern molecular mechanics (MM) programs have a graphics interface that allows the user to enter the structure by drawing it or by reading its Cartesian coordinates; the strain energy of the molecule in this given conformation can then be minimized. However, the resulting conformation is not necessarily the lowest energy (or global energy minimum) structure. In fact, it is quite possible that the minimized structure can be significantly higher in energy than the global minimum and therefore it may be of little practical importance.

The aim of a conformational search is to find as many minima as possible, including the global minimum, and to compute the Boltzmann population. In doing such a search, a large number of high energy starting conformations are generated, minimized, compared with previously found conformers, and stored if they are unique. For a thorough search, the crude starting geometries must span the entire potential energy surface; if only part of the surface is covered one cannot be sure that all important low energy minima will be found. Ideally, a grid or deterministic conformational search in which the starting conformations cover all of the conformational space should be conducted in all molecular simulations. However, for large and/or very flexible molecules, the CPU time required to explore the entire energy surface is prohibitive. It is more common to use stochastic or Monte Carlo methods, which employ a random element to generate starting geometries or to sample structures in a molecular dynamics (MD) run. Numerous conformational searching methods are presented in the literature. Some of them were designed for use on small cyclic and acyclic peptides and organic molecules,¹⁻³ while others were devised to search the conformational space available to small proteins,⁴ polymers,⁵ and carbohydrates.⁶ Comparisons of different search methods were published.⁷⁻⁹

Conformational searches of transition metal compounds are complicated by the fact that coordination compounds are often composed of multidentate ligands, resulting in many ring systems joined at the metal ion. Such metal ions can be found in a variety of coordination geometries (e.g., octahedral, trigonal prismatic, trigonal bipyrami-

dal, square pyramidal, square planar, tetrahedral, etc.), and transition metal compounds often adopt geometrical isomers that are not available to organic compounds.¹⁰ The effectiveness of the Monte Carlo method was recently compared to that of MD in searching the conformational space of cis-square planar platinum(II) antitumor drugs.¹¹ This was an important start to investigating conformational search methods for inorganic systems, but it concentrated on the flexible side chains of the complexes and not on the problems that are specific to coordination compounds. In this article we use two conformational searching methods to try and find all of the geometric and conformational isomers available to a series of three cobalt(III) test compounds.

INORGANIC MM

MM analyses of organic molecules, proteins, and nucleotides are very common.¹² Despite the fact that coordination compounds were among the first molecules to be modeled by MM,^{13,14} their analysis is less common.¹⁵⁻²² This is due to problems such as varied coordination geometries and the trans and Jahn-Teller effect in transition metal compounds. The fields of inorganic¹⁵⁻²² and bioinorganic^{23,24} MM were recently reviewed, and the methods used to overcome complications due to partially filled d orbitals were discussed.^{21, 25-27}

There are three common ways to model valence angle deformations around transition metals within the MM method.¹⁶⁻²²

In the electrostatic or ionic model, interactions between the metal and the ligands are taken to be purely ionic and there are no additional bond stretching or valence angle terms between them. This approach has been very successful with the more ionic compounds found with alkali and alkaline-earth metals,^{28,29} but it has been less successful with transition metal compounds where electronic effects are important. An advantage of the electrostatic model is that one set of parameters can model all coordination geometries. Its disadvantages include the necessity to obtain the "correct" charges for the metal ion and its coordinating ligands, along with having to use either dummy atoms or specific electronic terms in the modeling of square planar compounds.

In the valence force field model, the same potential functions used to model the organic ligand are used for metal-ligand interactions. Thus, metal-ligand stretching and ligand-metal-ligand

bending parameters are required. Torsions around the metal are usually set to zero. This is the most common method of modeling small coordination compounds. It requires many parameters including a separate set of parameters for each different geometry, and interconversion between geometries is impossible. The unique labeling problem must also be dealt with in this method.¹⁹

The points on a sphere (POS) approach is a mixed model in which a metal–ligand stretching function is used but the ligand–metal–ligand valence angle term is replaced by 1,3-nonbonded interactions for the coordinating atoms.^{16–22,30,31} This approach has the advantage of being able to model all coordination geometries with one set of parameters. Its only problem is that it does not incorporate electronic effects, such as those of a ligand field. For this reason, the method, for example, always minimizes four coordinate complexes to a tetrahedral not to a square planar geometry. This and other similar problems can be overcome by adding dummy atoms in the axial positions³² by out of plane or plane twist functions^{33–35} or by using an MM force field that has been enhanced by adding ligand field effects.^{25–27}

In order for a conformational search to find all geometric isomers of a transition metal compound, the valence angles around the metal have to be modeled with either the POS or ionic methods. This is because the valence force field model requires a separate set of parameters for each different geometry and set of geometric isomers; therefore, interconversion between geometric isomers is impractical with a valence force field.

To date, most published inorganic MM calculations have either ignored all isomers except the one of interest or have entered all the possible isomers graphically and minimized them individually.^{16–24} Because a random kick module was recently introduced into the MOMECS suite of programs and force field^{36,37} and the Monte Carlo dihedral and torsional variation method with the possibility of breaking metal ligand bonds has been included in MacroModel,³⁸ we decided to test the ability of these methods for inorganic conformational searches. Both programs model the geometry around the metal ion using a POS approach. In addition, MOMECS has, as a perturbation to this approach, a multiple harmonic valence angle potential with ligand field based force constants.²⁷ We also sampled structures from high temperature MD simulations to test their efficiency in inorganic conformational searching.

TEST SYSTEMS

As test systems we chose $[\text{Co}(\text{dien})_2]^{3+}$, $[\text{Co}(\text{dien})(\text{dpt})]^{3+}$, $[\text{Co}(\text{tet-a})\text{Cl}_2]^+$, and $[\text{Co}(\text{tet-b})\text{Cl}_2]^+$ (dien, diethylenetriamine; dpt, di(3-aminopropyl)-amine; tet-a, *meso*-5,5,7,12,12,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane; tet-b, *racemic*-5,5,7,12,12,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane). All test compounds have numerous conformations and have been well studied experimentally.^{21,39–47}

Cyclam derivatives such as tet-a and tet-b may coordinate in a planar (trans configuration of the two monodentate donors) or folded (cis configuration of the two monodentate donors) form (Fig. 1). In the following we consider the two ligands tet-a and tet-b as one species. The coordinated ligand has six chiral centers: the four coordinated amines (N1, N4, N8, N11) and the two methyl-substituted carbon atoms (C7 and C14; Fig. 2). This gives rise to 64 stereoisomers for the trans configuration of

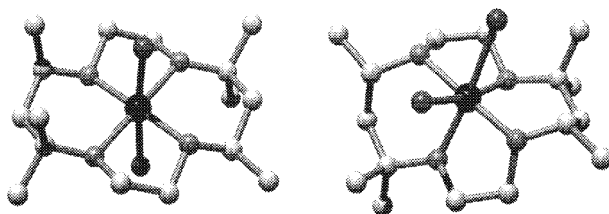


FIGURE 1. The lowest energy conformations of the trans III (left) and the cis V (right) configuration of $[\text{Co}(\text{tet-b})\text{Cl}_2]^{3+}$.

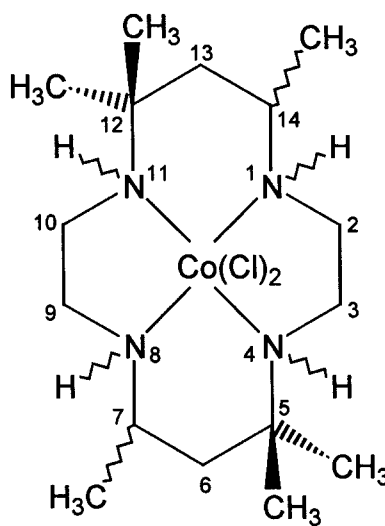


FIGURE 2. Configurations of $[\text{Co}(\text{L})\text{Cl}_2]^+$ (L, tet-a or tet-b).

the complex and to $2 \cdot 64$ stereoisomers of the cis configuration because there is no pseudosymmetry plane through the MN_4 fragment that relates the two monodentate donors. Not all of these configurations are nondegenerate; some are symmetry related. [Note that this analysis does not include different conformations due to the five-membered chelate rings (λ or δ ; Fig. 3) and the six-membered chelate rings (chair, twist boat).] The N-based configurations RSRS, RSRR, RSSR, RRSS, and RRRR (numbering in Fig. 2) are named trans I, trans II, trans III, trans IV, and trans V⁴⁸ and a similar nomenclature may be adapted for the cis configurations. Due to the corresponding pseudosymmetries of the square planar $[M(\text{tet-n})]$ fragment (only considering the N-configurations; C_{2v} , C_1 , C_i , C_2) the number of nondegenerate configurations for the trans geometry is 16; for the cis geometry there are 32 independent configurations. (Note again that the number of isomers is much larger due to the chelate ring conformations.)

The stereochemistry of $[\text{Co}(\text{dien})_2]^{3+}$ and its isomers has been extensively studied.^{21,39,40} The complex can adopt three different configurations that are known as the symmetrical-facial (s-fac), unsymmetrical-facial (u-fac), and meridional (mer) isomers, which are shown in Figure 4. The u-fac and mer-isomers are both chiral (C_2 symmetry

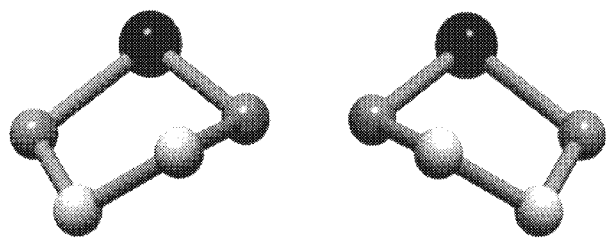


FIGURE 3. Conformations of the five-membered chelate rings: λ (left) and δ (right). The metal centers are black, the amine donors are dark grey, and the carbon atoms are light gray.

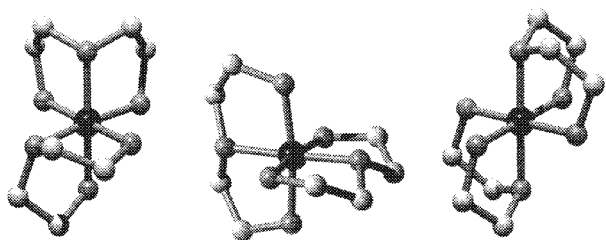


FIGURE 4. Configurations of $[\text{Co}(\text{dien})_2]^{3+}$ (and $[\text{Co}(\text{dien})(\text{dpt})]^{3+}$): u-fac (left), mer (middle), and s-fac (right).

each); the s-fac isomer has C_i symmetry and therefore is achiral. Assuming that each five-membered chelate ring can adopt a λ or δ conformation (i.e., ignoring envelope conformations), there are 48 possible conformations (for the three isomers, 15 are nondegenerate). The crystal structures of the mer,⁴¹ s-fac,⁴² and u-fac⁴³ isomers were determined, the relative stabilities of the three different isomers are known experimentally, and numerous MM analyses of $[\text{Co}(\text{dien})_2]^{3+}$ are available.^{21,44}

Due to the flexibility of the six-membered dpt rings and the lower symmetry of the three isomers, there are more conformations for the $[\text{Co}(\text{dien})(\text{dpt})]^{3+}$ system than for $[\text{Co}(\text{dien})_2]^{3+}$. For each of the mer, u-fac, and s-fac isomers, five-membered dien rings can adopt a λ or δ conformation and six-membered rings of dpt can be found in each conformation available to six-membered rings.⁴⁵ While MM and experimental data indicate that the mer isomer is the most stable isomer for the $[\text{Co}(\text{dien})_2]^{3+}$ system, the isomer distribution found for $[\text{Co}(\text{dien})(\text{dpt})]^{3+}$ suggests that the u-fac isomer is the most stable.⁴⁶ In an MM analysis of $[\text{Co}(\text{dien})(\text{dpt})]^{3+}$ the strain energy of 15 conformations was calculated and the u-fac isomer was found to be the most stable configuration.⁴⁷ In writing about $[\text{Co}(\text{dien})(\text{dpt})]^{3+}$ it was stated "In combination these conformations lead to a great many arrangements, and only a selection of these can be practicably considered by the molecular mechanics method."⁴⁷ This statement was based on the fact that in the past no conformational searches were undertaken in MM; instead all possible conformations were individually entered for minimization. Therefore, only conformations located in the vicinity of the initial structures were found. In this article we show that one step conformational searches, such as those investigated here, have the ability to find all the conformations available to inorganic complexes like $[\text{Co}(\text{dien})(\text{dpt})]^{3+}$.

CONFORMATIONAL SEARCH METHODS

The Monte Carlo dihedral and positional variation method uses internal coordinates, while the random kick method uses external coordinates. The advantage of using internal coordinates is that they cut down the molecular degrees of freedom. It is well known that valence angles and distances do not change much between the different conformations of a molecule and that the main changes are in the torsion angles. For this reason it is the torsion angles that are varied to obtain the crude

starting geometries in this Monte Carlo search method. In each Monte Carlo step a random number of flexible torsion angles are varied by a random amount, generating a new starting geometry that can be minimized. For cyclic systems the ring needs to be cleaved at one point so that all other torsions can be varied. To prevent the two ends of the cleaved ring from being too close or too far from each other, a ring closure constraint is set. The situation is more complicated for inorganic systems where coordination of multidentate ligands results in a number of adjoining ring systems and ring closure constraints can only be set for bonds that are not shared by other cyclic systems. The Monte Carlo dihedral angle variation method can be supplemented by Monte Carlo translational variations in which the position of individual atoms and/or molecular fragments are randomly moved and rotated.

In the Cartesian stochastic (or kick) Monte Carlo search method, a random kick is applied to each atom in the molecule, generating a new high energy starting geometry for energy minimization. In a conformational search of cycloheptadecane it was shown that the maximum kick size should be between 2.7 and 3.1 Å.⁹ Larger kicks distorted the molecule so badly that the average time for energy optimization was increased dramatically. The probability of falling back to the starting geometry increased when the kick size was smaller than 1.5 Å. The advantages of this method are that it can be applied to inorganic systems just as easily as to organic systems and it requires only eight lines of Fortran to implement.

MD searches have been shown to be less efficient at finding new minima than most conformational searching methods.⁹ This is particularly so when the minima are separated by large energy barriers, as can be expected for most of the inorganic geometric isomers that are formed by metal ligand bonds breaking and reforming. Therefore, we do not expect MD sampling to be an efficient inorganic conformational/geometric isomer searching method, but we are including MD sampling because the method was recently used in inorganic MM.⁴⁹

Experimental

Conformational searches conducted using the Monte Carlo dihedral and positional variation method^{50,51} were run with the MM2* force field in

MacroModel³⁸ version 5.5. The cobalt(III) parameters were identical to those used previously.⁵² All external torsion angles (i.e., dihedrals not involving the metal ion) were varied between 0° and 180°. Metal and monodentate ligands (if present) were translated by between 0 and 0.5 Å; ring closure atoms were defined with default constraints; and all bonds to the metal were broken to generate the translated multidentate ligand, metal, and monodentate ligand (if present) fragments. All multidentate ligand fragments were rotated by between 0° and 180° in each Monte Carlo step (see Fig. 5). The least used structure within 25 kJ/mol from the lowest energy structure was used as the starting structure for each new Monte Carlo step. All the structures generated in the searches of the Co(III) tet-a and tet-b complexes were converted from MacroModel to Hyperchem format using Babel. Hyperchem lite was used to determine the chirality of the six stereocenters in each of the 1000 structures.

Quenched MD were carried out with the MM2* force field in MacroModel³⁸ version 5.5. The cobalt(III) parameters were identical to those used

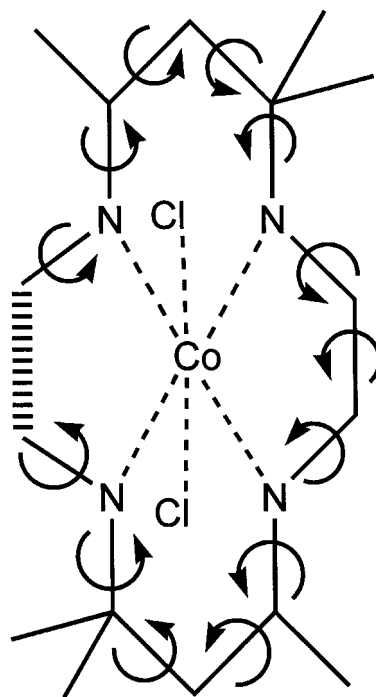


FIGURE 5. Monte Carlo dihedral and translational variation search of hexamethylcyclam: rotations are indicated by arrows; translation of the cobalt ion, chloride ions and the macrocycle, and rotation of the macrocycle. The bonds shown with dashed lines are temporarily broken and the thick dashed line is the closure bond.

previously in the Monte Carlo searches described above. All simulations were 500 ps with time steps of 1.00 fs at a temperature of 800 K. The temperature was controlled by a thermal bath with a 0.1-ps time constant, and all CH bond lengths were constrained by SHAKE. Structures were sampled every picosecond and minimized.

Calculations based on the random kick method were carried out using the MM program and force field MOMECE97^{36,37} with the recently introduced random kick module. Structures were generated by applying a random kick to all the atoms present in the original structure. The shift direction in spherical polar coordinates and kick distances were randomly chosen in each Monte Carlo step. A maximum shift of 3 Å for each atom was allowed. In each search 10,000 randomly modified starting structures were minimized individually. A structure was recognized as unique if any of the strain energies resulting from bond stretch, valence angle, torsion angle, or nonbonded interactions differed by more than 1.0 kJ/mol for the macrocyclic cobalt complex and 0.1 kJ/mol in the case of $[\text{Co}(\text{dien})_2]^{3+}$ and $[\text{Co}(\text{dpt})(\text{dien})]^{3+}$. The standard MOMECE force field was used as published.^{36,37} This involves 1,3-nonbonded interactions around the cobalt(III) center (POS) and a ligand field dependent (electronic) angle function (multiple harmonic potential).²⁷ The only parameters not available in the published force field are those involving Cl. The following ad hoc parameter set that leads to accurate structural predictions was used: $\text{Co}^{\text{III}}\text{-Cl}$, $k_b = 1.0 \text{ m dyn } \text{\AA}^{-1}$, $r_0 = 2.5 \text{ \AA}$; $\text{Cl-Co}^{\text{III}}\text{-Cl}$, $\text{Cl-Co}^{\text{III}}\text{-N}_{\text{amine}}$, $k_\theta = 0.0 \text{ m dyn } \text{\AA} \text{ rad}^{-2}$; $\theta_0 = 1.571 \text{ rad}$; Cl , $r_{\text{vdw}} = 1.95 \text{ \AA}$, $\epsilon = 0.240$. The results of the random kick/MOMECE searches were analyzed with a Microsoft EXCEL[®] macro that ordered all optimized structures as a function of the CIP descriptors for the stereocenters.

Results and Discussion

The aim of this study was to establish whether the two conformational search methods were able to find every geometrical isomer available to the test compounds. Although we do mention the order of stability of the different isomers, we were not interested in the relative energies or isomer distributions. (Note that different force fields were used for the two searching strategies.) However, it should be noted that with the MM2* force field the energy differences are systematically higher than

those calculated by MOMECE, and it seems that most MM2 derived force fields that have been modified for cobalt(III) compounds overestimate these energy differences.⁵³ Also, for the macrocyclic system, we do not concentrate here on a full conformational analysis.

In all three test cases the MD sampled structures found all conformational isomers of the five- and six-membered rings of the geometric isomer used in initiating the simulation. However, under the conditions studied the MD simulations were not able to invert tetrahedral nitrogen and carbon atoms and therefore could not change tet-a to tet-b, nor were they able to interconvert between the five configurations shown in Figure 2. Furthermore, MD simulations were not able to interconvert between the s-fac, u-fac, and mer isomers of the dien and dpt complexes.

BIS (DIETHYLENETRIAMINE) COBALT(III) COMPLEXES

One of the aims of the conformational searches of $[\text{Co}(\text{dien})_2]^{3+}$ and $[\text{Co}(\text{dien})(\text{dpt})]^{3+}$ was to find all possible combinations of the λ and δ conformations of the five-membered dien rings. This means that for each of the mer, u-fac, and s-fac configurations of $[\text{Co}(\text{dien})_2]^{3+}$ there should be 16 different combinations of λ and δ conformations. (Note that some of these isomers are stereoisomers and therefore degenerate; see above.) The Monte Carlo dihedral and positional variation method used a least squares atomic superimposition to find unique conformations and therefore found all stereoisomeric forms as unique structures. The random kick module used the energies of the complexes to establish whether a structure was unique; because stereoisomers have the same strain energy, only one stereoisomeric form was kept. Neither conformational search method found all 45 nondegenerate conformations. However, the reason for this was not that the conformational searches were incomplete. Minimizing the missing conformations showed that they were not energy minima and therefore were not found in the conformational search. This was noted earlier, based on a manual search of the conformational space.²¹

Both conformational searches found all three geometric isomers. Both force fields found only one s-fac structure; had a mer isomer as the lowest energy conformation, followed by a u-fac, and then an s-fac structure; had the same three lowest energy mer conformations ($\delta\lambda\text{-}\lambda\delta < \delta\delta\text{-}\lambda\delta < \delta\delta\text{-}\lambda\lambda$); and had a similar but not identical energetic

ordering of the u-fac isomers (MOMEC: $\delta\lambda\text{-}\lambda\delta < \delta\delta\text{-}\lambda\delta < \delta\delta\text{-}\delta\delta$; MM2*: $\delta\delta\text{-}\delta\delta < \delta\lambda\text{-}\delta\lambda < \delta\delta\text{-}\delta\lambda$).

Monte Carlo Dihedral and Translational Variation Method

The lowest energy conformations of the mer, u-fac, and s-fac isomers that were discussed in the previous paragraph were consistently found within 75 steps, no matter what starting conformation or isomer was used. In order to consistently find all of the same conformations within 50 kJ/mol of the lowest energy conformation, at least 500 Monte Carlo steps were required.

Random Kick Method

One thousand random kick steps were required to consistently find the lowest energy conformations. This was due to the relatively large number of starting structures, resulting from the kicks, that did not minimize.

(DIETHYLENETRIAMINE)- DI(3-AMINOPROPYL)AMINE] COBALT(III) COMPLEXES

The random kick search with the MOMEC97 force field found the three geometric isomers. Their stability was u-fac > s-fac > mer, which was predicted on the basis of the observed isomer distribution⁵⁴ and earlier MM calculations with a similar force field.⁴⁷ The Monte Carlo dihedral and translational variation method with the MM2* force field calculated the following stability order: mer > u-fac > s-fac.

Monte Carlo Dihedral and Translational Variation Method

A large number of the computed structures have at least one distorted ring system, and these are not easy to describe systematically; therefore, no attempt to list all of the conformations was made. As was the case for $[\text{Co}(\text{dien})_2]^{3+}$, the lowest strain energy conformations of the mer, u-fac, and s-fac isomers were consistently found within 75 kicks, no matter what starting conformation or isomer was used. Because it was extremely difficult to differentiate between many of the conformations, it was not possible to establish how many Monte Carlo steps were required to find all the conformations within 50 kJ/mol of the lowest energy conformation. This was due to the following:

the rings often adopted nonstandard conformations, there were many different low energy structures when the Monte Carlo dihedral and translational variation method translated and rotated ligands, the numbering schemes for the newly generated starting structures were different, and the least squares imposition algorithm used to find unique conformations was no longer effective (see Fig. 6).

Random Kick

Due to the increased number of possible conformations within the (3-aminopropyl)amine rings, a larger number of random kick steps was required to find the lowest energy conformations. At least 3000 random kicks were necessary to consistently reproduce this series from one single starting structure. Note that, in practice, separate searches starting from the three configurations (mer, s-fac, u-fac) would be recommended.

DICHLORO(5,5,7,12,12,14-HEXAMETHYL- 1,4,8,11-TETRAAZACYCLOOTETRADECANE) COBALT(III) COMPOUNDS

If the chirality of carbons 7 and 14 is not restrained, then a conformational search starting from $[\text{Co}(\text{tet-a})\text{Cl}_2]^+$ or $[\text{Co}(\text{tet-b})\text{Cl}_2]^+$ should find 16 trans isomers and 32 cis isomers (see above, conformations not included). Table I lists the lowest energy isomers in the order of increasing energy found by both search methods.

Monte Carlo Dihedral and Translational Variation Method

Five Monte Carlo searches of 1000 Monte Carlo steps were conducted, each starting with a different conformation. Because the search inverted the chirality of all the stereocenters and did not distinguish between degenerate structures (i.e., energy was not a criteria for structure selection), all 64 combinations should be found in the trans and

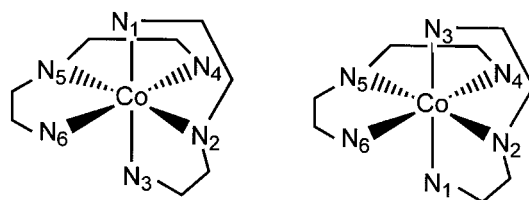


FIGURE 6. Two identical forms of $[\text{Co}(\text{dien})_2]^{3+}$ that indicate the artifact in the numbering inversion.

TABLE I.
Computed Isomer Distribution of [Co(tet-a)Cl₂]⁺
and [Co(tet-b)Cl₂]⁺.

[Co(tet-a)Cl ₂] ⁺	
Isomers (MM2*)	Isomers (MOMEC97)
Trans III	Trans III
Trans II	Trans II
Trans V	Trans I
Trans I	Trans V
Trans IV	Trans IV
Cis V	Cis V
Cis II	Cis II
Cis IV	Cis III
Cis I	Cis I
Cis III	Cis IV
[Co(tet-b)Cl ₂] ⁺	
Trans V	Trans II
Trans II	Trans I
Trans III	Trans IV
Trans I	Trans III
Trans IV	Trans V
Cis V	Cis V
Cis II	Cis II
Cis I	Cis IV
Cis III	Cis III
Cis IV	Cis I

On the left are all configurations found by the Monte Carlo searches using the MM2* force field and on the right are those determined by the random kick stochastic method using the MOMEC force field. The configurations are listed in the order of increasing energy.

both cis geometries. All stereocenters of all the structures in one of the runs were assigned their chirality. The search did not find the trans RRRRSS (SRSRRR), SRRRRS, RRSRSR, SSSRSR (RRSSSS), SRSSSR (RSSRSS), RSSSSS (SSSSSR), the cis with N1-Co-N8 = 90° RRSRSR, and the cis with N4-Co-N11 = 90° RRSRSR and SSRSRS stereochemistries (see Fig. 2 for atom numbering); these are all high energy configurations. The 250 lowest energy conformations from the other four searches were checked to see whether they had found the five trans configurations (trans I–V), the five cis configurations (cis I–V) with N1-Co-N8 = 90°, and the five cis configurations with N4-Co-N11 = 90°. All searches except one found all 15 configurations for both tet-a and tet-b. One of the searches failed to find the Co(III) tet-b trans V form.

The global energy minimum structure of [Co(tet-a)Cl₂]⁺ has a trans III configuration with both six-membered rings in a chair conformation

with equatorial 7,14-methyl groups and λδ five-membered rings. The lowest energy structure found for [Co(tet-b)Cl₂]⁺ has the cis V configuration, and both its six-membered rings are in a chair conformation with equatorial 7,14-methyl groups and δδ five-membered rings. In all five searches about 20% of the structures had an unrealistic geometry around the cobalt ion. This is due to the fact that the MM2* force field that was used has a cubic term to model the bond stretching energy that results in the energy going to $-\infty$ for the long bond lengths that can be obtained by a combination of dihedral and positional variations.

Random Kick Method

A total number of 10,000 random kick steps was carried out and all 16 trans isomers but only 17 of the 32 cis isomers were found. This occurred despite the fact that the energy limit for the determination of uniqueness of a minimized structure was set to 1 kJ/mol, which resulted in the finding of more than 500 minima. Some of the possible isomers were obtained with more than 50 “different” conformations while others only had one low energy conformation per configuration. Because the same starting geometry, a [Co(tet-a)Cl₂]⁺ trans III structure, was used for every cycle, more random kicks were required to bring the molecule into a cis rather than a trans configuration. Therefore, using different starting geometries with both cis and trans configurations or using directed starting geometries, that is, using the least used starting structure within 25 kJ/mol of the lowest energy structure, as was done in the Monte Carlo dihedral search should lead to more consistent results.

Conclusion

Our studies show that the Monte Carlo dihedral and translational variation search and the random kick Monte Carlo search are both significant improvements on the current method by which all possible isomers are entered graphically and minimized individually. The conformational search methods described here allow the inorganic MM practitioner to use a one-step procedure to find all low energy conformations, as well as all structural isomers. The techniques are much quicker at finding low energy conformations and structural isomers than the commonly used manual method. Furthermore, the Monte Carlo dihedral and trans-

lational variation method and the random kick approach are both capable of finding conformations that are far from ideal and that would not be found if all possible ideal isomers were entered and minimized individually.

The dihedral and translational variation Monte Carlo conformational searches were more efficient at finding all the possible conformations and geometric isomers than the random kick method. One disadvantage of the Monte Carlo conformational search technique, as implemented in MacroModel, is that the metal can be translated far enough from the ligating atoms so that the cubic MM2* stretching term starts decreasing with increasing metal to ligand distance, resulting in unnaturally long metal ligand bonds. Another disadvantage of the Monte Carlo conformational search method is that when it translates and rotates ligands, the numbering schemes for the newly generated starting structures are different and the least squares imposition algorithm used to find unique conformations is no longer effective (see Fig. 6).

The random kick method is a straightforward method and is very efficient, especially for smaller molecules, such as the cobalt bis(tri-amine) compounds. Using directed starting geometries, as was done in the Monte Carlo search, should lead to more consistent results.

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